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WHAT'S NEW IN INTENSIVE CARE

Lactate dynamics as a marker of perfusion: physiological interpretation and pitfalls

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Blood lactate concentration is among the most widely used biomarkers in intensive care; its elevation is traditionally viewed as a hallmark of impaired tissue oxygenation, with sustained hyperlactatemia being strongly associated with adverse outcomes in critically ill patients [1]. However, the regulation of lactate metabolism is more complex than a mere consequence of anaerobic glycolysis. As such, lactate dynamics, i.e., how levels evolve over time, provide **a** more nuanced insight into the patient's physiological status than single-point measurements. This viewpoint article examines the physiological basis, clinical relevance, and interpretive challenges of lactate monitoring in critical illness.

Lactate: beyond hypoxia

While lactate is also the end product of anaerobic metabolism, it is predominantly produced under aerobic conditions. Situations involving increased metabolic demand or adrenergic stimulation can lead to a surge in glycolytic flux that exceeds the oxidative capacity of the mitochondria, leading to the conversion of pyruvate to lactate despite adequate oxygen availability. This process, termed aerobic glycolysis, is commonly observed in sepsis, trauma, and other high-stress conditions [2]. Increased blood lactate concentrations may therefore arise from multiple mechanisms (electronic supplementary table 1), including tissue hypoxia due to reduced oxygen delivery or impaired extraction, enhanced glycolysis (driven by adrenergic activity, as in sepsis or after β_2-agonist administration, or increased metabolic activity, as during fever), reduced clearance (mainly in liver failure, but also secondary to renal and/or muscular dysfunction), or impaired tissue metabolism (mitochondrial dysfunction affecting pyruvate oxidation, such as in sepsis or drug intoxication) [3]. As such, elevated lactate levels can occur in the absence of tissue hypoperfusion, underscoring the need for careful contextual interpretation (clinical examination, organ dysfunction, other biomarkers of tissue hypoxia) to avoid diagnostic errors or misguided therapy.

Dynamic monitoring and trend analysis

Although isolated lactate levels on intensive care unit (ICU) admission have prognostic value [4], serial lactate measurements provide a more accurate assessment of patients' trajectories [5]. Lactate reduction (not "clearance", which would imply no further production of lactate but just its removal from the human body), which is typically assessed as a percentage over 6–24 h from baseline, is a stronger indicator of clinical improvement or deterioration. A rapid decline often signifies resolution of shock, restored tissue perfusion, or improved metabolic function [6]. Conversely, persistently elevated or rising levels may indicate ongoing tissue hypoperfusion, impaired cellular metabolism, and/or treatment failure [7]. In shock management, early lactate reduction $\geq$ 10–20% per hour has been linked to improved outcomes, often outperforming static threshold values [8]. Nonetheless, therapeutic efforts aimed solely at normalizing lactate can result in over-resuscitation, potentially leading to fluid overload or excessive vasopressor use [3]. Therefore, lactate reduction should also be interpreted within the broader clinical context (Fig. 1). For example, a septic patient whose blood lactate concentration decreases from 8.3 to 3.2 mmol/L following initial resuscitation, and in the absence of clinical signs of ongoing impaired tissue perfusion, should not receive additional

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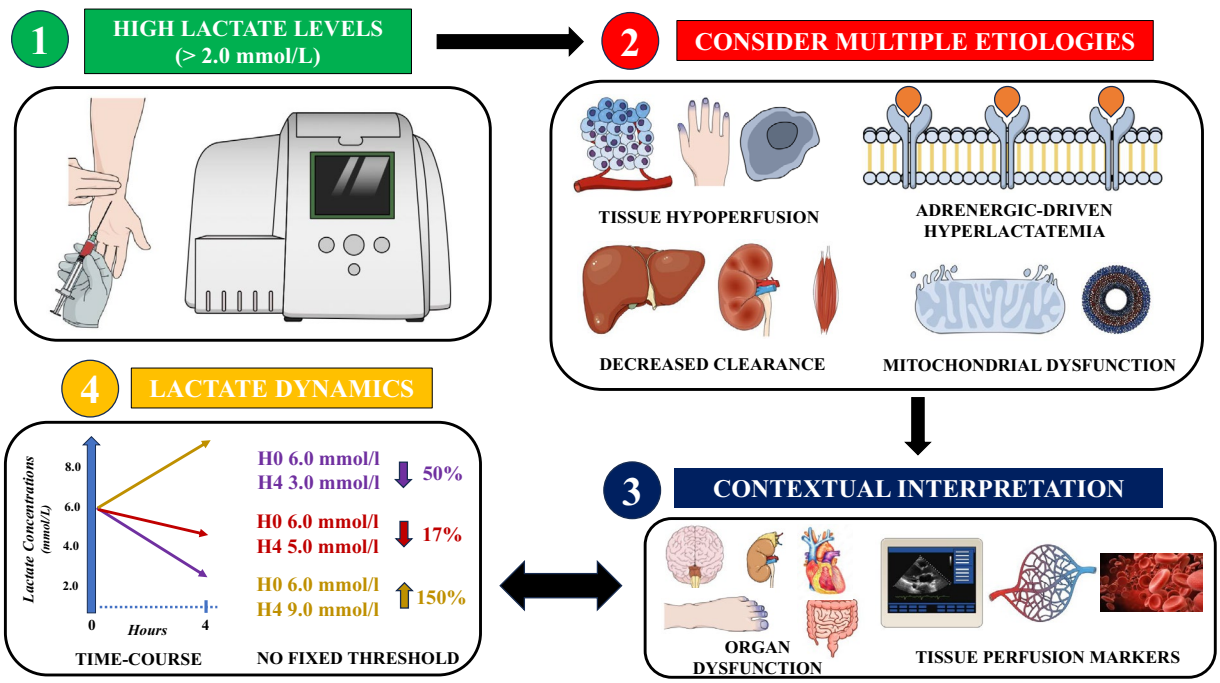

Fig. 1 Illustrates the multifactorial mechanisms underlying hyperlactatemia in critical illness and the importance of interpreting lactate values dynamically. Elevated blood lactate concentrations (> 2.0 mmol/L) may result from tissue hypoperfusion, adrenergic-driven aerobic glycolysis, reduced clearance (e.g., liver dysfunction), or mitochondrial impairment. Therefore, lactate must always be interpreted in its clinical context, in conjunction with markers of organ dysfunction and other indicators of tissue perfusion. No fixed threshold reliably distinguishes benign from pathological states. Instead, lactate dynamics, derived from serial measurements, provide more prognostic information. For example, a decrease from 6.0 to 3.0 mmol/l within 4 h reflects a favorable trajectory (50% reduction), whereas stable values (6.0 to 5.0 mmol/l, 17% reduction) or rising levels (6.0 to 9.0 mmol/l, 150% increase) indicate ongoing or worsening disease processes. Monitoring trends rather than isolated values enables a more nuanced and safer integration of lactate into shock management strategies

therapeutic interventions solely because lactate remains above 2.0 mmol/L. In such cases, a continued downward trend is likely, and further interventions may be unnecessary and potentially harmful. Importantly, lactate reduction may be delayed compared to improvements in other perfusion markers (such as $ScvO_2$ or PCO_2 gap), and clinicians should be aware of this temporal dissociation.

Lactate dynamics across different shock types (electronic supplementary table 1). The reduction in blood lactate concentrations may depend on the underlying type of shock. In septic shock, elevated lactate often reflects a combination of tissue hypoxia, hypermetabolism, and β-adrenergic stimulation. Declining levels typically indicate improving perfusion and resolution of stress responses [9]. In cardiogenic/obstructive shock, lactate rises primarily due to systemic hypoperfusion and remains a strong prognostic marker; reduction may be delayed despite hemodynamic stabilization, especially in the presence of hepatic congestion or depending on the resolution of the etiology (pulmonary embolism, cardiac tamponade) [10]. In hypovolemic shock, lactate correlates closely with circulatory status and usually normalizes quickly with appropriate volume replacement [11]. Of note, in patients undergoing renal replacement therapy (RRT), lactate may be artificially reduced depending on the membrane and flow characteristics, which complicates interpretation.

Common pitfalls in interpretation

A major pitfall is the systematic attribution of elevated blood blood lactate concentrations to tissue hypoxia, while other mechanisms (e.g., adrenergic-driven glycolysis) are frequent in critical illness [12]. Another common pitfall is the overreliance on blood lactate concentration as a sole marker of tissue perfusion. Regarding liver failure, although impaired clearance is often overemphasized, lactate elevation usually results from a combination of increased production and decreased clearance. Mild to moderate hepatic dysfunction alone rarely causes significant hyperlactatemia (>4 mmol/L) without concomitant increased production [13]. Finally, targeting lactate reduction as a rigid end point may lead to

over-resuscitation, exposing patients to the risks of fluid overload or excessive vasopressor administration. A safer approach is to integrate lactate trends with other clinical and hemodynamic markers (capillary refill time, $ScvO_2$, PCO_2 gap, skin perfusion) [7]

Complementary perfusion markers

Given its limitations, lactate should be used alongside other clinical indicators. Trials such as ANDROMEDA-SHOCK [14] suggest that targeting capillary refill time may match or exceed the efficacy of lactate-guided resuscitation strategies in septic shock. These bedside assessments often respond more rapidly to interventions and are less influenced by hepatic function or adrenergic tone. In addition, the veno-arterial PCO_2 gap combined with the $C(a\text{-}v)O_2$ ratio may help to discriminate hyperlactatemia related to tissue hypoxia from that due to non-hypoxic mechanisms [15]. Although the primary end point of ANDROMEDA-SHOCK was negative, post hoc analyses suggest that a lactate-guided strategy may still provide prognostic information and potential benefit when integrated into multimodal assessment.

Clinical integration

Fluid management strategy may also influence lactate dynamics, with restrictive versus liberal strategies showing differential effects on lactate reduction depending on the amount of infused fluids [16]. Effective use of lactate monitoring therefore involves a contextualized, trend-based approach: (a) prioritize longitudinal trends over isolated values; (b) correlate lactate with other perfusion markers and organ function; (c) consider non-hypoxic causes, such as stress responses or liver dysfunction; (d) avoid rigid normalization targets, tailoring interventions to the full clinical picture.

Conclusions

Lactate remains a cornerstone biomarker in critical care, but its interpretation requires a deep understanding of its physiological drivers. It reflects a complex interplay between perfusion, metabolism, organ function, and neurohormonal stress. Tracking lactate dynamics adds significant prognostic and diagnostic value, but clinicians must remain alert to non-hypoxic causes of elevation and resist the urge to over-treat based on lactate alone. A multimodal, nuanced approach ensures the most effective and patient-centered use of this important biomarker [17].

Supplementary Information
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